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| <p>(21) International Application Number: PCT/US98/03927 (22) International Filing Date: 6 March 1998 (06.03.98) (30) Priority Data: 08/814,899 12 March 1997 (12.03.97) US (71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): CHEN, Barbara, B. [US/US]; 1921 Robincrest Lane, Glenview, IL 60025 (US). CHEN, Helen [US/US]; 7 Baldwin Terrace, Livingston, NJ 07039 (US). RUSSELL, Mark, A. [GB/US]; 475 Cross Road, Gurnee, IL 60031 (US). (74) Agents: WILLIAMS, Roger, A. et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).</p> | | <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> |
| <p>(54) Title: LTA₄ HYDROLASE INHIBITORS</p> <p>(57) Abstract</p> <p>The present invention provides compounds having the structure: Ar₁-Q-Ar₂-O-(CH₂)_n-Z and pharmaceutically acceptable salts and stereoisomers thereof that are useful in the treatment of inflammatory diseases which are mediated by LTB₄ production, such as psoriasis, ulcerative colitis, IBD, and asthma.</p> | | |

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TITLE

LTA₄ HYDROLASE INHIBITORS

Field of the Invention

5 This invention relates generally to anti-inflammatory compounds and pharmaceutical compositions, and more particularly to anti-inflammatory compounds and compositions which are capable of inhibiting leukotriene A₄ hydrolase.

10

Background of the Invention

LTA₄ hydrolase is a requisite enzyme in the biosynthetic pathway leading to LTB₄ formation. LTB₄ is a
15 proinflammatory compound. R. Lewis, et al., *N. Engl. J. Med.* 323, 645-655 (1990) have demonstrated that LTB₄ is a potent granulocyte agonist inducing chemotaxis, aggregation, degranulation, adherence and priming of inflammatory cells for induction by other agonists.
20 Binding of LTB₄ to receptors is stereospecific with two distinct classes of binding sites. A. Lin, et al., *Prostaglandins* 28, 837-849 (1984). A high affinity site [$4-5 \times 10^{-10}$ M] mediates chemotaxis and chemokinesis while lower affinity sites [$0.6-5 \times 10^{-7}$ M] stimulate
25 granular secretion and oxidative burst. The LTB₄

receptor is associated with a GTP-binding protein that regulates affinity and transduces signals. T. Schepers, et al., *J. Biol. Chem.* 267, 159-165 (1992). Elevated LTB₄ levels have been reported for many diseases. Most prominently, elevated LTB₄ levels have been correlated to the pathology of inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis and in psoriasis. P. Sharon, et al., *Gastroent.* 86, 453-460; K. Lauritsen, et al., *Gastroent.* 95, 11-17 (1989); S. Brain, et al., *Br. J. Pharm.*, 83, 313-317 (1984). Other properties of LTB₄ which may contribute to disease processes are: stimulation of mucus secretion; stimulation of cytokine production; and the ability to act synergistically with other inflammatory mediators such as prostaglandins and cysteinyl leukotrienes thereby amplifying the inflammatory process.

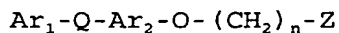
B. Samuelsson, et al., *J. Biol. Chem.*, 264, 19469-19472 (1989) have shown that LTB₄ biosynthesis from arachidonic acid involves the action of 2 enzymes, 5-lipoxygenase [5-LO] and LTA₄ hydrolase. 5-LO transforms arachidonic acid to 5-HPETE and subsequent formation of LTA₄, which is an unstable allylic epoxide intermediate which is enzymatically hydrolyzed by LTA₄ hydrolase to form the dihydroxy acid LTB₄.

LTA₄ hydrolase is distinct from cytosolic and microsomal epoxide hydrolases based on strict substrate requirements, product formation [5(S),12(R) vs. 5(S),6(R)] for mouse liver cytosolic epoxide hydrolase, and lack of inhibition by inhibitors of cytosolic epoxide hydrolase. LTA₄ hydrolase appears to be ubiquitously distributed in mammalian tissues even in cell types that do not express 5-LO, suggesting the importance of transcellular metabolism of LTA₄. While peptidomimetic compounds such as bestatin and captopril have been shown to exhibit LTA₄ hydrolase inhibitory

activity, they are not able to satisfy the requirement of a small organic compound which is capable of cellular penetration. It would therefore be very advantageous to be able to provide low molecular weight inhibitors of LTB₄ biosynthesis which preferably exhibit oral activity in vivo at desirably low concentrations.

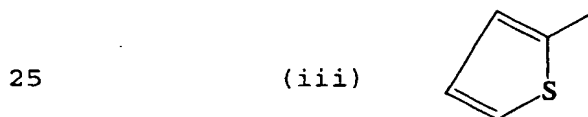
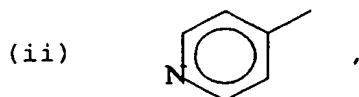
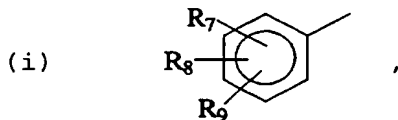
Summary of the Invention

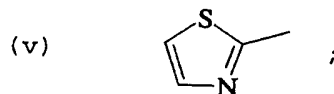
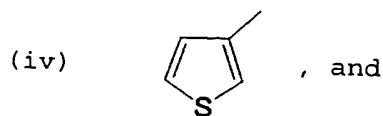
Applicants have now discovered that compounds having the structure:



and pharmaceutically acceptable salts and stereoisomers thereof possess LTA₄ hydrolase inhibitor activity, wherein

Ar¹ is an aryl moiety selected from the group consisting of:



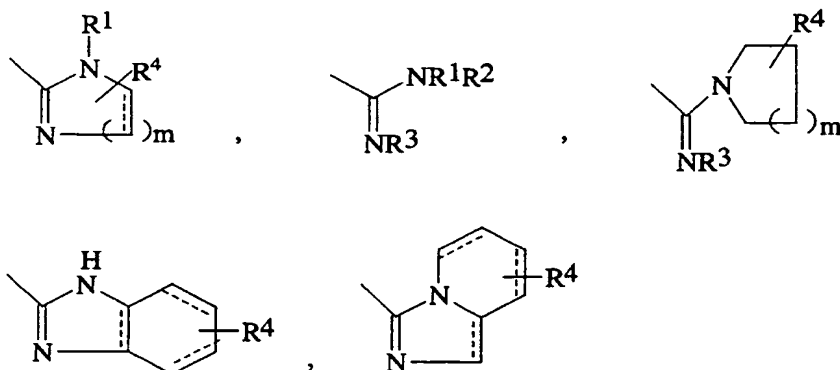


Ar² is an aryl moiety selected from the group
consisting of phenyl, mono-, di-, and tri-
substituted phenyl, wherein the substituents are
selected from the group consisting of Cl, Br, F,
CF₃, lower alkyl, lower alkoxy, NH₂, NO₂, and OH;
Q is selected from the group consisting of:

- (i) -O-;
(ii) -CH₂-,
(iii) -OCH₂-,
(iv) -CH₂O-,
(v) -NH-;
(vi) -NHCH₂-,
(vii) -CH₂NH-,
(viii) -CF₂-,
(ix) -CH=CH-,
(x) -CH₂CH₂-, and
(xi) carbon-carbon single bond;

n = 1, 2 or 3;

Z is



wherein

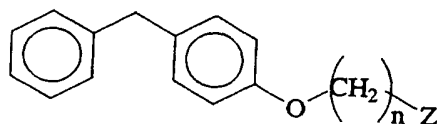
- 5 R^1 , R^2 and R^3 are independently H, OH, lower alkyl, lower alkoxy, allyl, cyclic alkyl or $(CH_2)_p-CO_2R^5$ wherein p is an integer from 1 to 6;
- R^4 is H, CO_2R^5 , $CONH_2$, or $COOH$;
- 10 R^5 is H, lower alkyl, lower alkoxy, allyl or benzyl; ----- represents a single or double bond; and
- m is 1 or 2.

15 Detailed Description

In one of its embodiments, the present invention entails compounds having the structure:



- and pharmaceutically acceptable salts and stereoisomers thereof, wherein Ar_1 , Q, Ar_2 , Z, and n are as defined
- 25 hereinbefore. In a preferred embodiment, the compounds of the present invention have the structure:



5 The compounds of the present invention, in several embodiments, may comprise a carboxylic acid or ester moiety. It will be appreciated by those of ordinary skill in the art

10 that a compound of the present invention comprising an ester moiety is readily converted, *in vivo*, especially when administered orally, into its corresponding carboxylic acid form. The ester-containing compounds of the present invention are therefore prodrugs of their carboxylic acid form.

15 In another of its aspects, the invention entails a pharmaceutical composition comprising a pharmacologically effective amount of one or more of the compounds defined above and a pharmaceutically acceptable carrier.

20 In still another of its embodiments the present invention involves a method for treating a mammal exhibiting an LTB₄ mediated inflammatory condition comprising administering to the mammal a
25 pharmacologically effective amount of one or more of the compounds defined above.

30 The term "lower alkyl" means straight or branched chain alkyl having 1 to 6 carbon atoms such as methyl, ethyl, propyl, butyl, pentyl, hexyl and the branched chain isomers thereof. The term "lower alkoxy" means straight or branched chain alkoxy having 1 to 6 carbon

atoms such as methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy and the branched chain isomers thereof. The term "cyclic alkyl" as used herein refers to non-aromatic alkyl ring structures, including multi-ring
5 structures such as bicyclic and tricyclic rings, having between 5 and 20 carbon atoms. The term "allyl" as used herein means the 1-propenyl radical, $-\text{CH}_2-\text{CH}=\text{CH}_2$. The term "halo" or "halogen" means fluoro, chloro, bromo, or iodo.

10

Included within the classes and subclasses of compounds defined above are isomeric forms of the described compounds including diastereoisomers, enantiomers and tautomeric forms of the described compounds.

15 Pharmaceutically acceptable salts of such compounds are also included as well as pharmaceutically acceptable salts of such isomers and tautomers.

20 In the structures disclosed herein, a bond drawn across a bond in a ring indicates that the bond can be to any available atom of the ring structure.

The expression "pharmaceutically acceptable salts" is intended to include those salts capable of being formed
25 with the compounds of the present invention without materially altering the chemical structure or pharmacological properties thereof. Such salts can be inorganic and organic cations or acid addition salts, and included, but are not limited to, sodium,
30 potassium, calcium, ammonium, alkylammonium, quaternary ammonium, triethanolamine, lysine, hydrochloride, hydrobromide, and others well known to those of ordinary skill in the art. The foregoing salts are prepared in the conventional manner by neutralization
35 of the compounds defined above with the desired base or acid.

The compounds of the present invention can be administered to a subject in such oral dosage forms as tablets, capsules, pills, powders, granules, elixirs or syrups, as well as aerosols for inhalation. Likewise, administration may be effected intravascularly, subcutaneously, or intramuscularly using dosage forms known to those of ordinary skill in the pharmaceutical arts. In general, the preferred form of administration is oral. An effective but non-toxic amount of the compound is employed in treatment. The dosage regimen utilizing the present compounds is selected in accordance with a variety of factors including the type, age, weight, sex and medical condition of the patient; the severity of the condition to be ameliorated; and the route of administration. A physician of ordinary skill can readily determine and prescribe a "pharmaceutically effective amount" of one or more of the compounds defined above, that is, the effective amount of a compound required to prevent, treat or arrest the progress of the condition. Dosages of the compounds of the present invention will range generally between 0.1 mg/kg/day to about 100 mg/kg/day and preferably between about 0.5 mg/kg/day to about 50 mg/kg/day when administered to a subject suffering from allergic or hypersensitivity reactions or inflammation. The compounds may also be administered transdermally or topically to treat proliferative skin conditions such as psoriasis. The daily dosage may be administered in a single dose or in equal divided doses, for example, three to four times daily. The "subject" is typically a mammal and, in particular, a human patient.

As used herein the phrase "LTA₄ hydrolase inhibitor" means a compound that is capable of exhibiting an IC₅₀ of less than 1 mM in an in vitro assay employing 10 µg/ml of LTA₄ hydrolase enzyme (specific activity 600

nMoles LTB₄/min/mg of enzyme) in the presence of 25 μ M substrate (LTA₄) in a total reaction volume of 100 μ l.

In the pharmaceutical compositions and methods of the present invention, at least one of the active compounds defined above or a pharmaceutically acceptable salt thereof will typically be administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier materials") suitably selected with respect to the intended form of administration and consistent with conventional pharmaceutical practices. For example, the pharmaceutical compositions of this invention can be administered as oral tablets, capsules, elixirs, syrups and the like. For oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol and the like; for oral administration in liquid form, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier such as ethanol and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Lubricants for use in these dosage forms include boric acid, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methylcellulose, agar, bentonite, guar gum and the like.

By virtue of their activity as LTA₄ hydrolase inhibitors, the compounds defined above are useful in treating inflammatory conditions mediated by LTB₄ production in mammals such as psoriasis, contact and atropic dermatitis, Crohn's disease, ulcerative colitis, inflammatory bowel disease, multiple sclerosis, ankylosing spondylitis, arthritis, asthma and the like. Similarly, the compounds defined above can be used in preventing recurring inflammatory attacks. A physician or veterinarian of ordinary skill can readily determine whether a subject exhibits the inflammatory condition. A preferred utility relates to treatment of ulcerative colitis.

Among the compounds of the present invention are the following:

- α-[4-(phenylmethyl)phenoxy]methyl]-1-piperidinemethanimine, monohydrochloride;
- α-[4-(phenylmethyl)phenoxy]methyl]-1-pyrrolidinemethanimine, monohydrochloride;
- ethyl 1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidinecarboxylate, monohydrochloride;
- ethyl 3-[[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]amino]propanoate, monohydrochloride;
- 4,5-dihydro-2-[4-(phenylmethyl)phenoxy]methyl]-1H-imidazole;
- 1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidinecarboxamide;
- 1-imino-2-[4-(phenylmethyl)phenoxy]ethanamine;
- α-[3-[4-(phenylmethyl)phenoxy]propyl]-1-piperidinemethanimine, monohydrochloride;
- 4,5-dihydro-2-[3-[4-(phenylmethyl)phenoxy]propyl]-1H-imidazole;
- 3a,4,5,6,7,7a-hexahydro-2-[4-(phenylmethyl)phenoxy]propyl]-1H-benzimidazole;

2-[4-(phenylmethyl)phenoxy]-N-(tricyclo[3.3.1.1
3,7]decan-2-yl)ethanimidine, monohydrate;

N'-hydroxy-2-[4-(phenylmethyl)phenoxy]ethanimidamide.

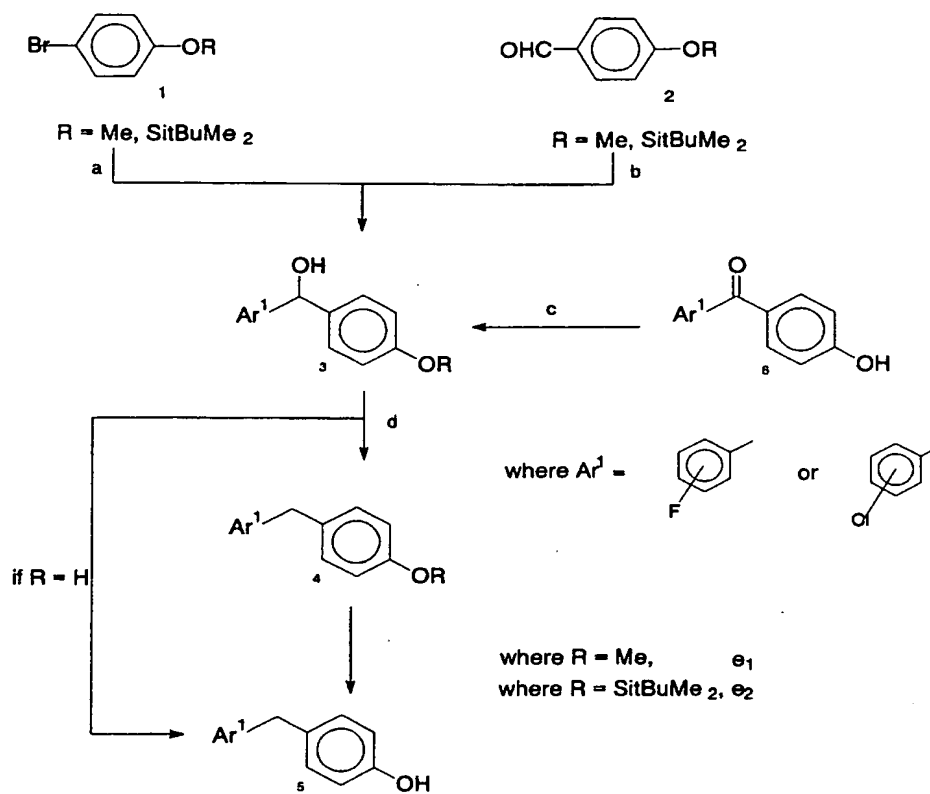
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The compounds of the invention are prepared from readily available starting materials by any of the following alternate processes in a conventional manner. The following reaction schemes describe methods which can be employed for preparing the compounds defined above, including starting materials, intermediates and reaction conditions. The following terms, as used herein, have the following definitions:


| | | |
|----|----------------------|---|
| 15 | NMMO | N-methylmorpholine-N-oxide |
| | Me | methyl |
| | SitBuMe ₂ | t-butyldimethylsilyl |
| | nBuLi | n-butyllithium |
| | THF | tetrahydrofuran |
| 20 | Et ₂ O | diethyl ether |
| | EtOH | ethyl alcohol |
| | Pd/C | palladium on carbon |
| | TFA | trifluoroacetic acid |
| | Et ₃ SiH | triethylsilane |
| 25 | TBAF | tetrabutylammonium fluoride |
| | DMF | dimethylformamide |
| | nBu ₄ NBr | tetra-n-butylammonium bromide |
| | TsCl | tosylchloride or p-toluenesulfonyl-chloride |
| 30 | TsO | tosylate or p-toluenesulfonate |
| | MeOH | methyl alcohol |
| | AcOH | acetic acid |
| | Bn | benzyl |
| | DEAD | diethylazodicarboxylate |
| 35 | Ph ₃ P | triphenylphosphine |
| | MCPBA | metachloroperbenzoic acid |
| | LAH | lithium aluminum hydride |
| | TsOH | tosic acid or p-toluenesulfonic acid |
| | LDA | lithium diisopropylamide |

| | | |
|----|----------------------------------|---------------------------|
| | DSC | disuccinylcarbonate |
| | nBuOH | n-butyl alcohol |
| | TFAA | trifluoroacetic anhydride |
| | Me ₃ SnN ₃ | trimethyl-tin azide |
| 5 | TMS | trimethyl silyl |
| | Ac ₂ O | acetic anhydride |
| | Ac | acetate |
| | EtOAc | ethyl acetate |
| | Hep | heptane |
| 10 | | |

Scheme 1

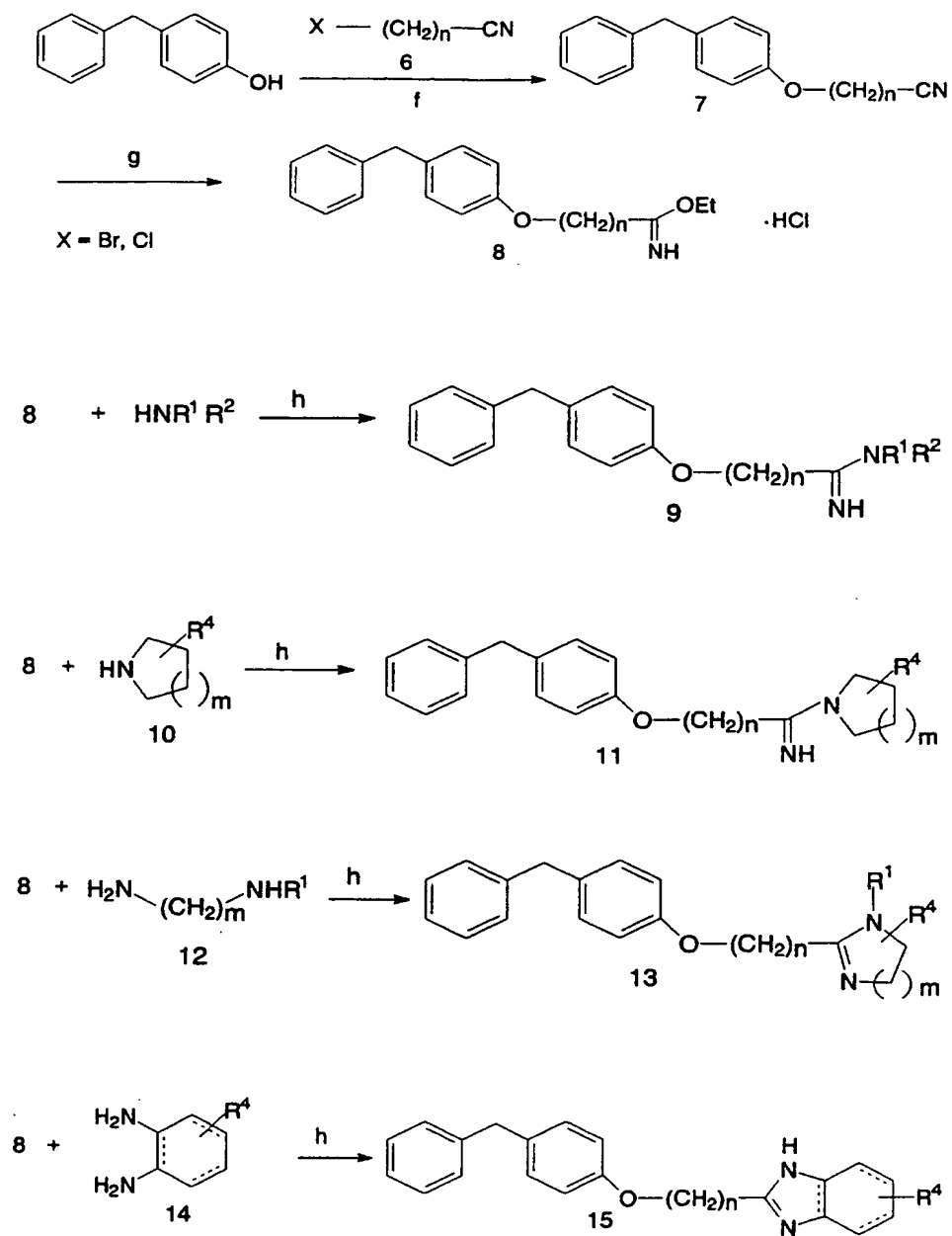


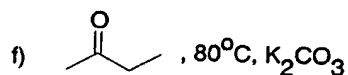
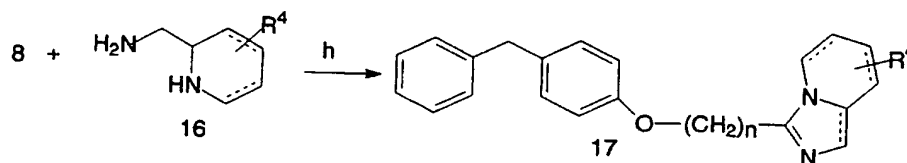
- a) nBuLi, THF, -78°C; Ar¹CHO.
b) Ar¹Li or Ar¹MgBr, Et₂O, -78°C.
c) EtOH, NaBH₄.
d) EtOH, 4% Pd/C, H₂ or CH₂Cl₂, TFA, Et₃SiH.
e¹) BrBr₃, CH₂Cl₂, -78°C.
e²) THF, TBAF.

Scheme 1 shows methods for producing compounds having the structure $\text{Ar}^1\text{---CH}_2\text{---}$  ---OH . Scheme 1 shows

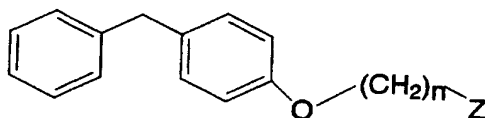
two related precursor compounds (1, 2) which may be employed as a starting material. Compound 1 is an alkylated or silylated derivative of p-bromophenol. A convenient starting material 1 is 1-bromo,4-methoxybenzene (i.e., R is methyl). On the other hand, compound 1 may be readily provided by silylation of p-bromophenol with t-butyldiphenylsilyl chloride or other silylating agents. In either event, compound 1 may be reacted with tert-butyl lithium in an ethereal solvent at low temperature, such as in THF at -78°C , and quenched with an arylaldehyde (Ar^1CHO) to yield compound 3. Similarly, starting from compound 2, a p-methoxybenzaldehyde or a silylated derivative of p-hydroxybenzaldehyde may be employed. Compound 2 may be reacted with an aryl lithium (Ar^1Li) or aryl magnesium bromide (Ar^1MgBr) to yield compound 3. Regardless of which route is chosen, compound 3 is reduced, e.g., by hydrogenation over palladium on carbon or with triethylsilane, to provide compound 4. Compound 4 is readily deprotected using TBAF in THF (desilylation) or using BBr_3 in methylene chloride at -78°C (dealkylation) to provide compound 5, 4-hydroxydiphenylmethane.

Scheme 2





Scheme 2 shows methods for preparing compounds having
5 the general formula:

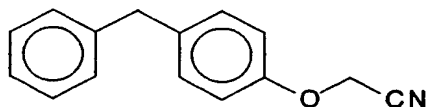


10 wherein Z and n are as defined hereinbefore.

4-hydroxydiphenylmethane may be reacted with an
alkylnitrile halide of compound 6 in the presence of a
base, for example, K₂CO₃, in a solvent, for example,
15 methyl ethyl ketone, and reflux at 80°C for 18 hours to
yield compound 7. Addition of dry hydrogen chloride to
compound 7 in ethanol may provide imidates, compound 8.
Compound 8 may be reacted with ammonia or primary or
secondary amines, in ethanol, to afford amidines,
20 compound 9. Compound 8 may be also reacted with
compounds 10, 12, 14 and 16 to generate corresponding
compounds 11, 13, 15 and 17, wherein R¹, R², R⁴, n and m
are as defined hereinbefore.

Example 1

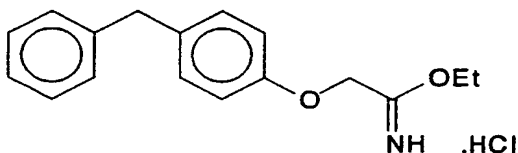
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10 To a stirred solution of 4-hydroxydiphenylmethane (20 g, 0.11 mol) in methyl ethyl ketone (100 mL) was added chloroacetonitrile (8.3 g, 0.11 mol) and potassium carbonate (50 g, 0.36 mol) and the mixture was refluxed at 80°C for 18 hours. The solvent was removed under
15 reduced pressure. The residue was taken up in water, extracted twice with ether and the combined organic layers were washed 4 times with 5% NaOH, water and brine, and then dried (Na₂SO₄) and concentrated in vacuo to give the title compound as brown oil (23.5 g). The
20 resulting product was fully characterized in the next step (Example 2).

Example 2

25



30

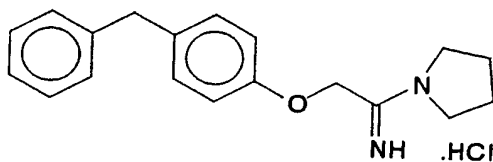
To a stirred solution of the compound of Example 1 (23.5 g, 0.1 mol) in chloroform (60 mL) was added absolute ethanol (5 g, 0.11 mol) and the solution was cooled in the reaction flask on an ice bath. A stream
35 of hydrogen chloride gas was introduced into the reaction mixture until the required amount of HCl (4 g, 0.11 mol) was absorbed. The flask was tightly sealed and stored in the refrigerator overnight. A white solid was filtered and washed several times with ether
40 and then recrystallized from ethanol/ether to afford the

title compound as white crystals (15 g). The product had the following properties:

Analysis calculated for $C_{17}H_{20}NO_2Cl + 0.3H_2O$: Calc: C, 65.61; H, 6.67; N, 4.50. Found: C, 65.63; H, 6.41; N, 4.47.

Example 3

α -[[4-(phenylmethyl)phenoxy)methyl]-1-pyrrolidinemethanimine, monohydrochloride



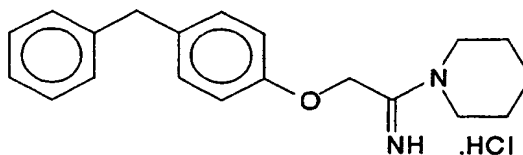
To a solution of the compound of Example 2 (1 g, 3.3 mmol) in ethanol (5 mL) was added pyrrolidine (306 mg, 4.3 mmol) and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the solid was recrystallized from ethanol/ether to give the title compound as white crystals (520 mg). The product had the following properties:

Analysis calculated for $C_{19}H_{23}N_2OCl + 0.3H_2O$: Calc: C, 67.87; H, 7.07; N, 8.33. Found: C, 67.91; H, 6.93; N, 8.27.

Example 4

α -[[4-(phenylmethyl)phenoxy)methyl]-1-piperidinemethanimine, monohydrochloride

5



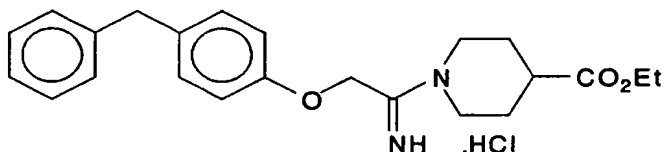
10 This compound was prepared by the method given in Example 3 using piperidine in place of pyrrolidine to afford the title compound as white crystals. The product had the following properties:

15 Analysis calculated for $C_{20}H_{25}N_2OCl$: Calc: C, 69.65; H, 7.31; N, 8.12. Found: C, 69.29; H, 7.12; N, 7.93.

Example 5

20 ethyl 1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidinecarboxylate, monohydrochloride

25

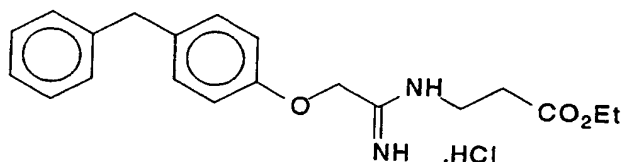


This compound was prepared by the method given in Example 3 using ethyl isonipecotate in place of pyrrolidine to afford the title compound as white
30 crystals. The product had the following properties:

Analysis calculated for $C_{23}H_{29}N_2O_3Cl$: Calc: C, 66.26; H, 7.01; N, 6.72. Found: C, 65.86; H, 6.98; N, 6.63.

Example 6

ethyl 3-[[[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]amino]propanoate,
monohydrochloride



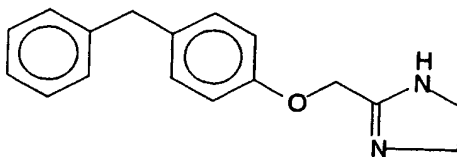
10

To a solution of the compound of Example 2 (0.5 g, 1.6 mmol) in ethanol (5 mL) was added beta-alanine ethyl ester hydrochloride (307 mg, 2.0 mmol) and triethylamine (202 mg, 2 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue was dissolved in ethanol and ether was added until a white solid formed. The mixture was filtered and the filtrate was concentrated and purified by preparatory silica gel plates eluting with $\text{CHCl}_3/\text{EtOH}/\text{NH}_4\text{OH}$ (84/15/1) to give the title compound as white crystals (30 mg). The product had the following properties:

Analysis calculated for $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_3\text{Cl} + 0.9 \text{ H}_2\text{O}$: Calc: C, 61.11; H, 6.87; N, 7.13. Found: C, 61.04; H, 6.38; N, 7.27.

Example 7

4,5-dihydro-2-[[4-(phenylmethyl)phenoxy]methyl]-1H-imidazole



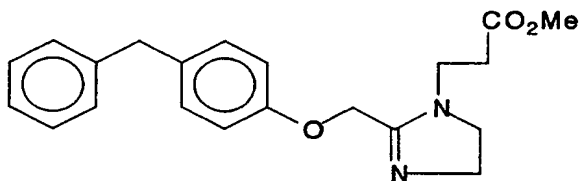
35

To a stirred solution of the compound of Example 2 (0.5 g, 1.6 mmol) in ethanol (5 mL) was added ethylenediamine (1 mL). The mixture was refluxed under

argon for 8 hours and then cooled to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in methanol. Ether was added until a white precipitate formed which was filtered, and the filtrate was concentrated and then purified by preparatory silica gel plates eluting with $\text{CHCl}_3/\text{EtOH}/\text{NH}_4\text{OH}$ (84/15/1) to give the title compound as a white solid (180 mg). The product had the following properties:

Analysis calculated for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O} + 0.5 \text{ H}_2\text{O}$: Calc: C, 74.16; H, 6.95; N, 10.17. Found: C, 74.01; H, 6.69; N, 10.10.

Example 8



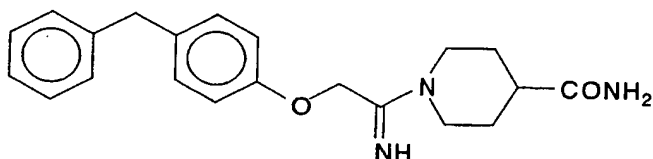
To a solution of the compound of Example 7 (70 mg, 0.26 mmol) in CH_2Cl_2 (2 mL) was added methyl acrylate (27 mg, 0.31 mmol). The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by preparatory silica gel plates eluting with $\text{CHCl}_3/\text{EtOH}/\text{NH}_4\text{OH}$ (90/10/0.5) to afford the title compound as yellow oil (15 mg). The product had the following properties:

Analysis calculated for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_3 + 1.1 \text{ H}_2\text{O}$: Calc: C, 67.76; H, 7.09; N, 7.53. Found: C, 67.75; H, 6.96; N, 7.50.

Example 9

1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidinecarboxamide

5



- 10 To a stirred solution of the compound of Example 2 (305 mg, 1 mmol) in ethanol (3 mL) and methanol (3 mL) was added isonipecotamide (128 mg, 1 mmol). The mixture was refluxed under argon overnight. Then the reaction mixture was cooled to room temperature and the solvent
- 15 was removed under reduced pressure. The residue was dissolved in 1N NaOH and extracted three times with CH_2Cl_2 . The combined organic layers were washed with water, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The solid was recrystallized from
- 20 methanol/ether to give the title compound as white crystals (80 mg). The product had the following properties:

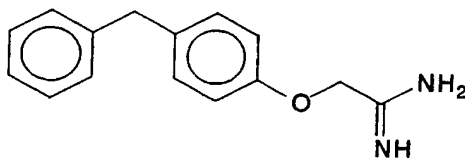
Analysis calculated for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_2 + 0.3 \text{ H}_2\text{O}$: Calc: C, 70.68; N, 7.23; N, 11.78. Found: C, 70.82; H, 6.60; N, 11.82.

25

Example 10

1-imino-2-[4-(phenylmethyl)phenoxy]ethanamine

30



35

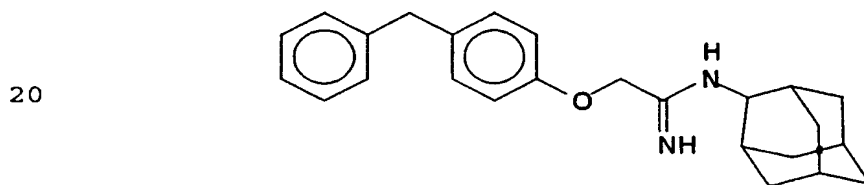
To a solution of the compound of Example 2 (305 mg, 1 mmol) in ethanol (3 mL) was added a solution of 9% NH_3 in ethanol (0.3 mL), and the mixture was stirred at

room temperature overnight. The mixture containing a white precipitate was filtered and the filtrate was concentrated. The residue was dissolved in 1N NaOH and extracted three times with CH_2Cl_2 . The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The white solid obtained was triturated with ether to give pure title compound which had the following properties:

Analysis calculated for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O} + 0.1 \text{ H}_2\text{O}$: Calc: C, 74.42; H, 6.74; N, 11.57. Found: C, 74.51; H, 6.67; N, 11.49.

Example 11

2-[4-(phenylmethyl)phenoxy]-N-(tricyclo[3.3.1.1^{3,7}]decan-2-yl)ethanimidamide, monohydrate



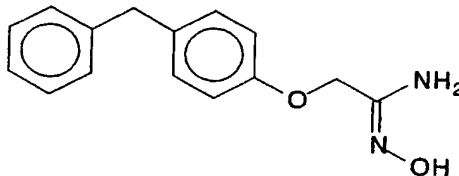
To a solution of the compound of Example 2 (458 mg, 1.5 mmol) in ethanol (10 mL) was added 2-adamantanamine hydrochloride (281 mg, 1.5 mmol) and triethylamine (152 mg, 1.5 mmol), and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with $\text{CHCl}_3/\text{EtOH}/\text{NH}_4\text{OH}$ (92/7/0.5) to give the title compound as yellow solid (320 mg). The product had the following properties:

Analysis calculated for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O} + 1 \text{ H}_2\text{O}$: Calc: C, 76.50; H, 8.22; N, 7.14. Found: C, 76.43; H, 7.90; N, 7.11.

Example 12

N'-hydroxy-2-[4-(phenylmethyl)phenoxy]ethanimidamine

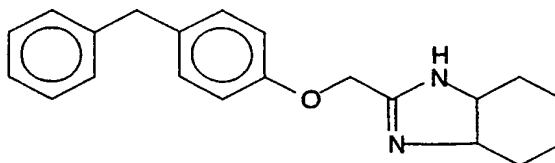
5



To a stirred solution of the compound of Example 1 (1g, 4.5 mmol) in ethanol (20 mL) was added hydroxylamine hydrochloride (312 mg, 4.5 mmol) and triethylamine (454 mg, 4.5 mmol) and the mixture was refluxed for 4 hours. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in water and extracted three times with ether. The combined organic layers were dried (Na₂SO₄), filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with hexane/ethyl acetate (4/1) to give the title compound as yellow crystals. (0.5 g). The product had the following properties:

Analysis calculated for C₁₅H₁₆N₂O₂: Calc: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.51; H, 6.30; N, 10.81.

Example 13

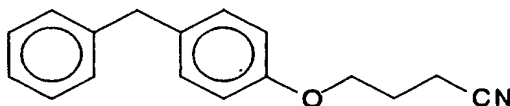


5

To a stirred solution of the compound of Example 2 (0.5 g, 1.6 mmol) in ethanol (5 mL) was added 1,2-
10 diaminocyclohexane (182 mg, 1.6 mmol) and the mixture was refluxed for 5 hours. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by preparatory silica gel plates eluting with
15 $\text{CHCl}_3/\text{EtOH}/\text{NH}_4\text{OH}$ (90/10/1) to give the title compound as yellow oil (100 mg). The product had the following properties:

Analysis calculated for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O} + 0.9 \text{ H}_2\text{O}$: Calc: C, 74.92; H, 7.72; N, 8.32. Found: C, 74.82; H, 7.77; N, 8.24.

Example 14



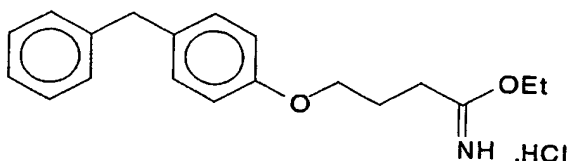
25

The method described in Example 1 was employed, except
30 that 4-bromobutyronitrile was used in place of chloroacetonitrile, to afford the title compound as a yellow oil. The resulting product was fully characterized in the next step (Example 15).

35

Example 15

5



The method described in Example 2 was carried out using the compound of Example 14 in place of the compound of Example 1 to afford the title compound as white
10 crystals. The product had the following properties:

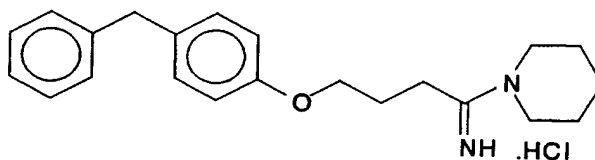
Analysis calculated for $C_{19}H_{24}NO_2Cl$: Calc: C, 68.36; H, 7.25; N, 4.20. Found: C, 68.43; H, 6.90; N, 4.10.

15

Example 16

α -[3-[4-(phenylmethyl)phenoxy]propyl]-1-peperidinemethanimine, monohydrochloride

20



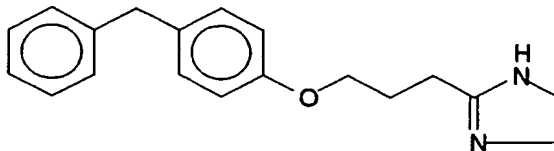
The method described in Example 3 was carried out using
25 the compound of Example 15 in place the compound of Example 2 to afford the title compound as white crystals. The product had the following properties:

Analysis calculated for $C_{22}H_{29}N_2OCl$: Calc: C, 70.85; H, 7.84; N, 7.51. Found: C, 70.59; H, 7.90; N, 7.61.
30

Example 17

4,5-dihydro-2-[[4-(phenylmethyl)phenoxy]
methyl]-1H-imidazole

5



To a stirred solution of the compound of Example 15
10 (0.5 g, 1.5 mmol) in ethanol (5 mL) was added
ethylenediamine (1 mL) and the mixture was refluxed
under argon for 8 hours. The mixture was cooled to room
temperature and the solvent was removed under reduced
pressure. The residue was dissolved in 5% K₂CO₃ and
15 extracted three times with CH₂Cl₂. The combined organic
layers were washed with water and brine, dried with
Na₂SO₄, filtered and concentrated in vacuo. The residue
was purified by preparatory silica gel plates eluting
with 2% NH₄OH/MeOH to give the title compound as yellow
20 solid (50 mg). The product had the following
properties:

Analysis calculated for C₁₉H₂₂N₂O + 0.4 H₂O: Calc: C,
75.67; H, 7.62; N, 9.29. Found: C, 75.68; H, 7.58; N,
25 9.20.

LTA Hydrolase Methods

The following Table presents data demonstrating the
30 pharmacological activity of the LTA hydrolase
inhibitors of the present invention. One or more of
three different assays, (1) an in vitro LTA hydrolase
enzyme assay, (2) a human whole blood assay utilizing
calcium ionophore stimulation, and (3) a murine ex vivo
35 assay utilizing calcium ionophore stimulation were
employed to determine the level of LTA hydrolase
inhibitor activity.

Recombinant Human LTA Hydrolase Assay for LTA Hydrolase Inhibitor Activity

Compounds of the present invention were tested for LTA
5 hydrolase inhibitor activity against recombinant human
LTA hydrolase (rhLTAH). Recombinant human LTA
hydrolase-encoding vectors were prepared and used to
express rhLTAH essentially as described by J. Gierse,
et al., *Protein Expression and Purification*, 4, 358-366
10 (1993). Briefly, LTA hydrolase encoding DNA was
amplified by polymerase chain reaction using a pair of
oligonucleotide primers based on the nucleotide
sequence from the 5'-end, and the complement of the 3'-
end, of the coding region of the LTA hydrolase gene,
15 the nucleotide sequence of which gene is known. (See,
C. Funk, et al., *Proc. Natl. Acad. Sci. USA* 84, 6677-
6681 (1987)). A λ gt11 human placental cDNA library
(Clontech, Palo Alto, CA) provided the nucleic acid
template. The LTA hydrolase encoding region had a
20 length of about 1.9 kb. The amplified 1.9 kb DNA was
isolated and cloned into the genomic baculovirus,
Autographa californica nuclear polyderosis virus
(AcNPC) DNA, and the baculovirus expression vector was
transfected into *Spodoptera frugiperda* Sf-9 cells
25 employing the calcium phosphate co-precipitation method
(see, M. Summers, et al., *Tex. Agric. Exp. Stn. Bull.*
1555, 1-57 (1987)). Recombinant LTA₄ hydrolase enzyme
was purified from the transfected Sf-9 cells
essentially as described by J. Gierse, et al., *supra*.

30 One or more predetermined amounts of a compound of the
invention were incubated in assay buffer (0.1 M
potassium phosphate, 5 mg/ml fatty acid free BSA, 10%
DMSO, pH 7.4) for 10 minutes at room temperature with
35 250 ng of recombinant hLTA₄H to allow binding, if any,
between the enzyme and inhibitor. The stock enzyme
solution was 1 mg/ml LTA₄ hydrolase, 50 mM Tris, pH

8.0, 150 mM NaCl, 2.5 mM beta-mercaptoethanol, 50% glycerol. The specific activity of the enzyme was about 650 nMoles/min/mg. LTA₄ (i.e., substrate) was prepared from the methyl ester of LTA₄ (Biomol, Inc.,
5 Plymouth Meeting, PA) by treating the methyl ester with 30 molar equivalents of LiOH at room temperature for 18 hours. The LTA₄ substrate in its free acid form was kept frozen at -80°C until needed. LTA₄ (free acid) was thawed and diluted in assay buffer (minus DMSO) to a
10 concentration of 350 ng/ml and 25 µl (8ng) of LTA₄ substrate was added to the reaction mixture (total volume of reaction mixture = 200 µl at time zero. Each reaction was carried out at room temperature for 10 minutes. The reaction was stopped by diluting 25 µl of
15 the reaction mixture with 500 µl of the assay buffer without DMSO. LTA₄ was quantified in the diluted sample by a commercially available enzyme-linked immunoassay [Caymen Chemical Co. Ann Arbor, MI] using the method recommended in the manufacturer's instructions and
20 compared to the amount of LTA₄ produced in a negative control (i.e., essentially identical conditions except without addition of an inhibitor compound). The IC₅₀ was routinely calculated from the data produced.

25 **LTB₄ and Thromboxane Production by Calcium Ionophore Stimulated Human Blood for LTB₄ Hydrolase Inhibitor Activity**

Human blood, collected in heparin-containing Vacutainer
30 tubes, was diluted 1:4 with RPMI-1640 media and 200 µl of the diluted blood was added into each of a 96-well microtiter plate. One or more concentrations of the leukotriene A₄ hydrolase inhibitor compounds being tested were prepared (diluted in DMSO) and 2 µl added
35 and gently mixed with the diluted whole blood. After incubating for 15 minutes at 37°C in a humidified incubator, calcium ionophore A13187 (Sigma Chemical

Co., St. Louis, MO) was added to a final concentration of 20 mcg/ml and the incubation continued under the same conditions for an additional 10 minutes to allow LTB₄ formation. The reaction was terminated by
5 centrifugation (833 g, 10 minutes at 4°C) and supernatant were analyzed for LTB₄ and thromboxane by commercially available enzyme-linked immunoassays (Caymen Chemical Co., Ann Arbor, MI) according to the manufacturer's instructions. The IC₅₀ of each test
10 compound was determined from the amount of inhibition of LTB₄ production as compared to an essentially identical assay in which no inhibitor compound was present.

15 **Ex Vivo LTB₄ and Thromboxane Production by Calcium Ionophore Stimulated Mouse Blood for LTB₄ Hydrolase Inhibitor Activity**

Leukotriene A₄ hydrolase inhibitor compounds of the
20 present invention were diluted to a predetermined concentration in phosphate buffered saline containing 2% DMSO and 1% Tween 80. The compounds were administered by oral gavage to adult male outbred mice weighing approximately 20-30 gm at a dose of 10 mg/kg
25 body weight. (Compounds given at a dose of 50 mg/kg body weight are designated in following Table by the symbol, *) Sixty (60) minutes after administration of an LTA₄ inhibitor compound of the invention, blood was collected (into heparin-containing tubes) from the
30 retroorbital sinus. The heparinized blood was added to the wells of a microtiter plate along with an equal volume of RPMI-1640 media, and calcium ionophore A23187 was added to a final concentration of 20 mcg/ml. The mixture was incubated for 10 minutes at 37°C in a
35 humidified incubator. The reaction was terminated by centrifugation (833 g. 10 minutes at 4°C). Supernatant were analyzed for LTB₄ and thromboxane by commercially

available enzyme-linked immunoassays [Caymen Chemical Co., Ann Arbor, MI] in accordance with the manufacturer's instructions. The percent inhibition was determined by comparison to animals treated identically except that the solution administered by oral gavage was devoid of inhibitor compound.

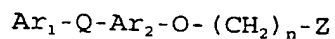
LTA₄ HYDROLASE INHIBITOR ACTIVITY

| Ex. # | Recombinant Human LTA ₄ Hydrolase Assay IC ₅₀ LTA ₄ (μM) | Inhibition of Calcium Ionophore-induced LTB ₄ Production in Human Blood IC ₅₀ HWB (μM) | Murine Ex Vivo LTB ₄ Inhibition %I LTB ₄ /at 1 hour after administration of 10mg/kg |
|-------|--|---|--|
| 3 | 0.004 | 0.053 | 46 |
| 4 | 0.0043 | 0.085 | 30 |
| 5 | 0.0013 | 0.071 | 62 |
| 6 | 0.023 | 0.2 | 54 |
| 7 | 0.07 | 0.22 | 33 |
| 8 | 1.17 | 0.55 | 68 |
| 9 | 0.017 | 0.077 | 30 |
| 10 | 0.089 | 0.48 | 0 |
| 11 | 7.8 | - | - |
| 12 | >100 | 17.9 | 63 |
| 13 | 0.2 | 0.19 | 71 |
| 16 | 0.053 | 0.64 | 60 |
| 17 | 0.064 | 0.64 | 28 |

"-" means Not Determined

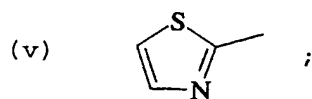
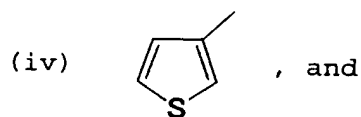
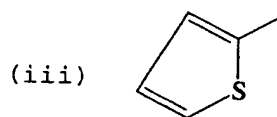
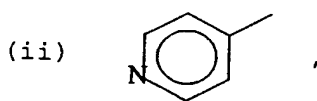
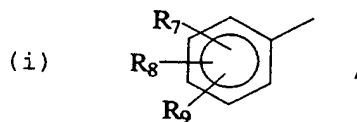
What is claimed is:

1. A compound having the structure:



and pharmaceutically acceptable salts and stereoisomers thereof possess LTA₄ hydrolase inhibitor activity, wherein

Ar¹ is an aryl moiety selected from the group consisting of:



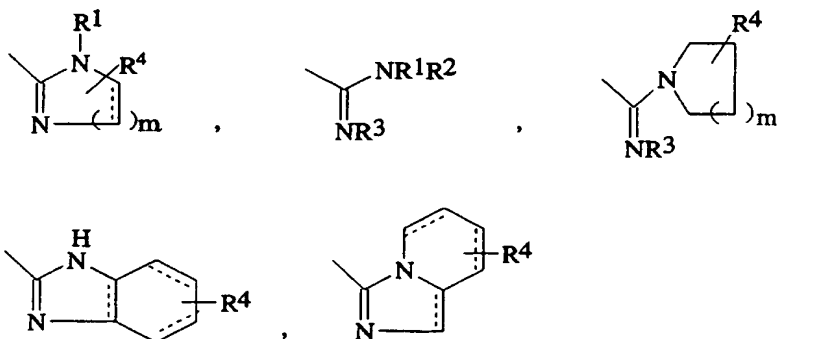
Ar² is an aryl moiety selected from the group consisting of phenyl, mono-, di-, and tri-substituted phenyl, wherein the substituents are

selected from the group consisting of Cl, Br, F, CF₃, lower alkyl, lower alkoxy, NH₂, NO₂, and OH;
Q is selected from the group consisting of:

- (i) -O-;
- (ii) -CH₂-;
- (iii) -OCH₂-;
- (iv) -CH₂O-;
- (v) -NH-;
- (vi) -NHCH₂-;
- (vii) -CH₂NH-;
- (viii) -CF₂-;
- (ix) -CH=CH-;
- (x) -CH₂CH₂-, and
- (xi) carbon-carbon single bond;

n is 1, 2, or 3; and

Z is



wherein

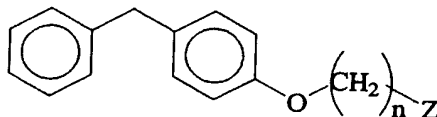
R¹, R² and R³ are independently H, OH, lower alkyl, lower alkoxy, allyl, cyclic alkyl or (CH₂)_p-CO₂R⁵ wherein p is an integer from 1 to 6;

R⁴ is H, CO₂R⁵, CONH₂, or COOH;

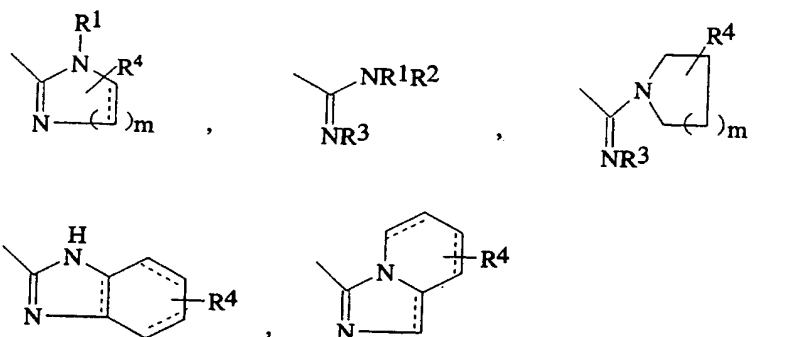
R⁵ is H, lower alkyl, lower alkoxy, allyl or benzyl;

----- represents a single or double bond;
and m is 1 or 2.

2. The compound of claim 1 having the structure:



and pharmaceutically acceptable salts and stereoisomers thereof, wherein n is 1, 2, or 3 and Z is



wherein

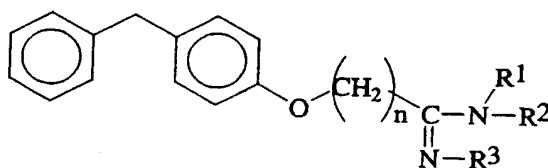
R^1 , R^2 and R^3 are independently H, OH, lower alkyl, lower alkoxy, allyl, cyclic alkyl or $(CH_2)_p-CO_2R^5$ wherein p is an integer from 1 to 6;

R^4 is H, CO_2R^5 , $CONH_2$, or $COOH$;

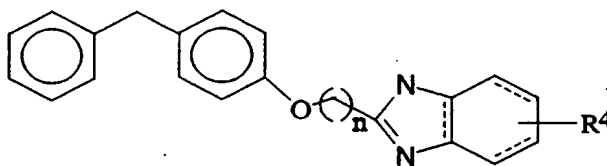
R^5 is H, lower alkyl, lower alkoxy, allyl or benzyl;

----- represents a single or double bond;
and m is 1 or 2.

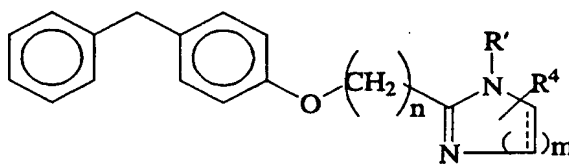
3. The compound of claim 2 having the structure



4. The compound of claim 2 wherein R^2 is $(CH_2)_m CO_2 R^5$.
5. The compound of claim 4 wherein n is 1 and m is 2.
6. The compound of claim 2 wherein R^1 and R^2 are independently hydrogen, lower alkyl, or cyclic alkyl.
7. The compound of claim 5 wherein R^3 is hydrogen or hydroxyl.
8. The compound of claim 2 which has the structure:

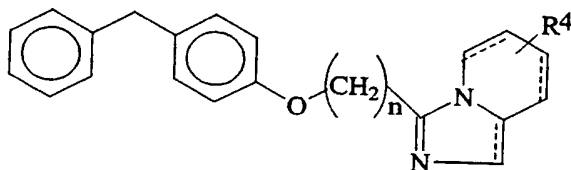


9. The compound of claim 8 wherein R^4 is H or $CO_2 R^5$ wherein R^5 is hydrogen, lower alkyl or benzyl.
10. The compound of claim 2 which has the structure:



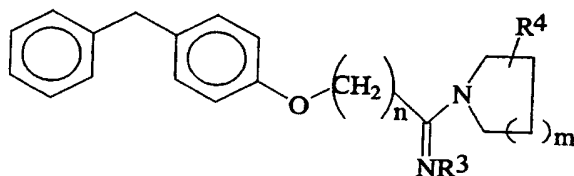
11. The compound of claim 10 wherein R^4 is H or $CO_2 R^5$ wherein R^5 is hydrogen, lower alkyl or benzyl.

12. The compound of claim 2 which has the structure:



13. The compound of claim 12 wherein R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

14. The compound of claim 2 which has the structure:



15. The compound of claim 14 wherein R^3 is hydrogen or hydroxyl and R^4 is H, CONH_2 , or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

16. The compound of claim 2 chosen from the group consisting of:

α -[[4-(phenylmethyl)phenoxy]methyl]-1-piperidinemethanimine, monohydrochloride;

α -[[4-(phenylmethyl)phenoxy]methyl]-1-pyrrolidinemethanimine, monohydrochloride;

ethyl 1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidinecarboxylate, monohydrochloride;

ethyl 3-[[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]amino]propanoate, monohydrochloride;

4,5-dihydro-2-[4-(phenylmethyl)phenoxy]methyl]-1H-imidazole;

1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidinecarboxamide;

1-imino-2-[4-(phenylmethyl)phenoxy]ethanamine;

α -[3-[4-(phenylmethyl)phenoxy]propyl]-1-piperidinemethanimine, monohydrochloride;

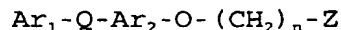
4,5-dihydro-2-[3-[4-(phenylmethyl)phenoxy]propyl]-1H-imidazole;

3a,4,5,6,7,7a-hexahydro-2-[4-(phenylmethyl)phenoxy]propyl]-1H-benzimidazole;

2-[4-(phenylmethyl)phenoxy]-N-(tricyclo[3.3.1.1^{3,7}]decan-2-yl)ethanimidine, monohydrate;

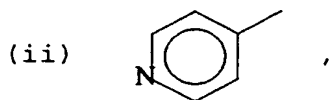
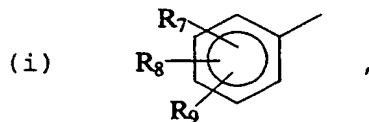
N'-hydroxy-2-[4-(phenylmethyl)phenoxy]ethanimidamide.

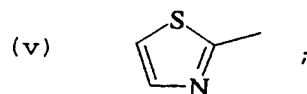
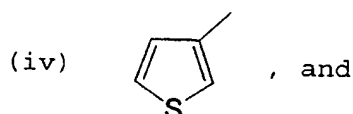
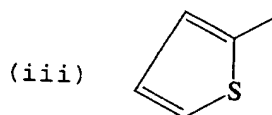
17. A pharmaceutical composition comprising a compound having the structure



and pharmaceutically acceptable salts and stereoisomers thereof, and a pharmaceutically acceptable carrier, wherein

Ar¹ is an aryl moiety selected from the group consisting of:



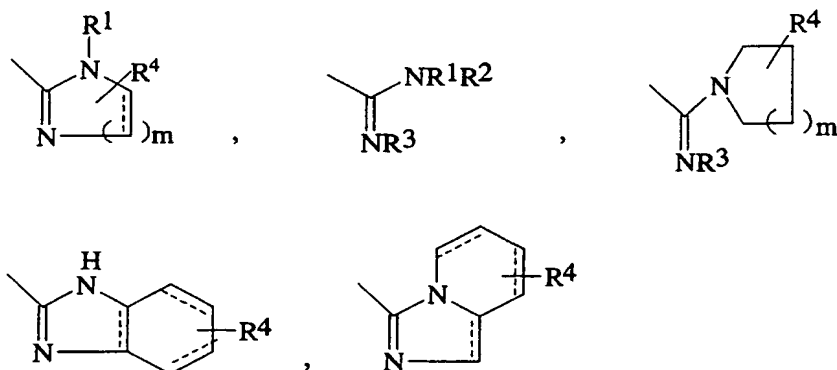


Ar² is an aryl moiety selected from the group consisting of phenyl, mono-, di-, and tri-substituted phenyl, wherein the substituents are selected from the group consisting of Cl, Br, F, CF₃, lower alkyl, lower alkoxy, NH₂, NO₂, and OH; Q is selected from the group consisting of:

- (i) -O-;
- (ii) -CH₂-;
- (iii) -OCH₂-;
- (iv) -CH₂O-;
- (v) -NH-;
- (vi) -NHCH₂-;
- (vii) -CH₂NH-;
- (viii) -CF₂-;
- (ix) -CH=CH-;
- (x) -CH₂CH₂-, and
- (xi) carbon-carbon single bond;

n is 1, 2, or 3; and

Z is



wherein

R^1 , R^2 and R^3 are independently H, OH, lower alkyl, lower alkoxy, allyl, cyclic alkyl or $(CH_2)_p-CO_2R^5$ wherein p is an integer from 1 to 6;

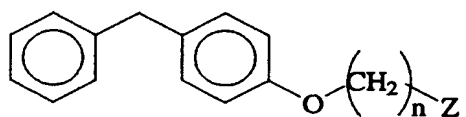
R^4 is H, CO_2R^5 , $CONH_2$, or $COOH$;

R^5 is H, lower alkyl, lower alkoxy, allyl or benzyl;

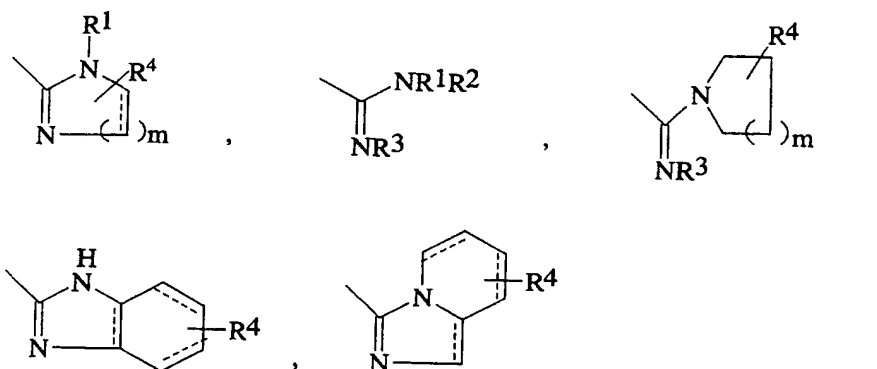
----- represents a single or double bond;

and m is 1 or 2.

18. The pharmaceutical composition of claim 17 wherein the compound has the structure:



wherein n is 1, 2, or 3 and Z is



wherein

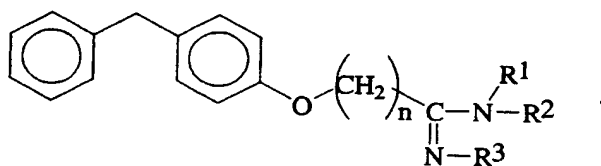
R^1 , R^2 and R^3 are independently H, OH, lower alkyl, lower alkoxy, allyl, cyclic alkyl or $(CH_2)_p-CO_2R^5$ wherein p is an integer from 1 to 6;

R^4 is H, CO_2R^5 , $CONH_2$, or $COOH$;

R^5 is H, lower alkyl, lower alkoxy, allyl or benzyl;

----- represents a single or double bond;
and m is 1 or 2.

19. The pharmaceutical composition of claim 17 wherein the compound has the structure:



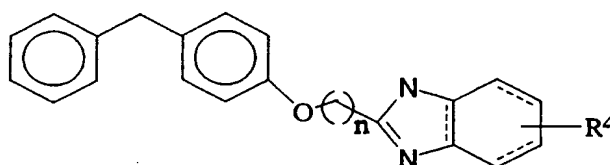
20. The pharmaceutical composition of claim 19 wherein in the compound R^2 is $(CH_2)_mCO_2R^5$.

21. The pharmaceutical composition of claim 20 wherein in the compound n is 1 and m is 2.

22. The pharmaceutical composition of claim 21 wherein in the compound R^1 and R^2 are independently hydrogen, lower alkyl, or cyclic alkyl.

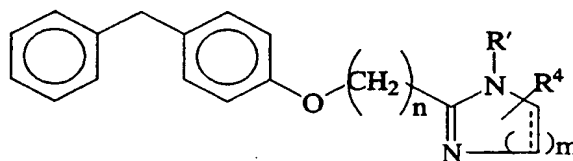
23. The pharmaceutical composition of claim 22 wherein in the compound R^3 is hydrogen or hydroxyl.

24. The pharmaceutical composition of claim 17 wherein the compound has the structure:



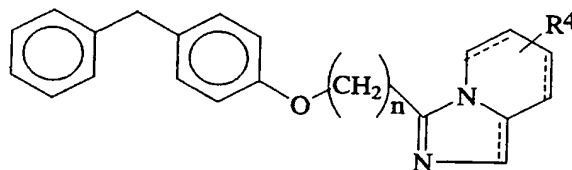
25. The pharmaceutical composition of claim 24 wherein in the compound R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

26. The pharmaceutical composition of claim 17 wherein the compound has the structure:



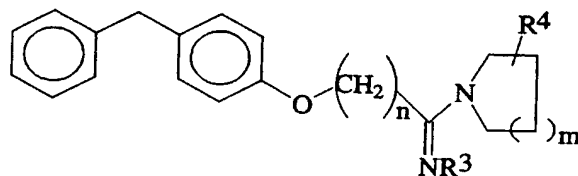
27. The pharmaceutical composition of claim 26 wherein in the compound R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

28. The pharmaceutical composition of claim 17 wherein the compound has the structure:



29. The pharmaceutical composition of claim 28 wherein in the compound R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

30. The pharmaceutical composition of claim 17 wherein the compound has the structure:



31. The pharmaceutical composition of claim 30 wherein in the compound R^3 is hydrogen or hydroxyl and R^4 is H, CONH_2 , or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

32. The pharmaceutical composition of claim 17 wherein the compound is chosen from the group consisting of:

α -[[4-(phenylmethyl)phenoxy]methyl]-1-piperidinemethanimine, monohydrochloride;

α -[[4-(phenylmethyl)phenoxy]methyl]-1-pyrrolidinemethanimine, monohydrochloride;

ethyl 1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidinecarboxylate, monohydrochloride;

ethyl 3-[[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]amino]propanoate, monohydrochloride;

4,5-dihydro-2-[[4-(phenylmethyl)phenoxy]methyl]-1H-imidazole;

1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidinecarboxamide;

1-imino-2-[4-(phenylmethyl)phenoxy]ethanamine;

α -[3-[4-(phenylmethyl)phenoxy]propyl]-1-piperidinemethanimine, monohydrochloride;

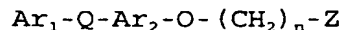
4,5-dihydro-2-[3-[4-(phenylmethyl)phenoxy]propyl]-1H-imidazole;

3a,4,5,6,7,7a-hexahydro-2-[[4-(phenylmethyl)phenoxy]propyl]-1H-benzimidazole;

2-[4-(phenylmethyl)phenoxy]-N-(tricyclo[3.3.1.1^{3,7}]decan-2-yl)ethanimidine, monohydrate;

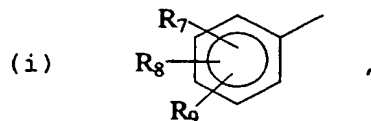
N'-hydroxy-2-[4-(phenylmethyl)phenoxy]ethanimidamide.

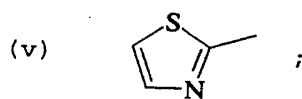
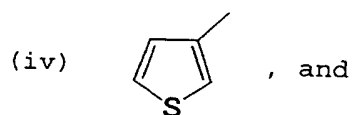
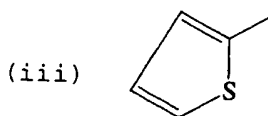
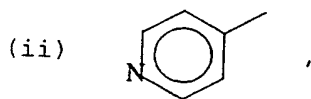
33. A method for treating an LTB₄-mediated inflammatory disease comprising administering to a mammal in need of treatment a therapeutically effective amount of a compound having the structure:



and pharmaceutically acceptable salts and stereoisomers thereof, and a pharmaceutically acceptable carrier, wherein

Ar¹ is an aryl moiety selected from the group consisting of:



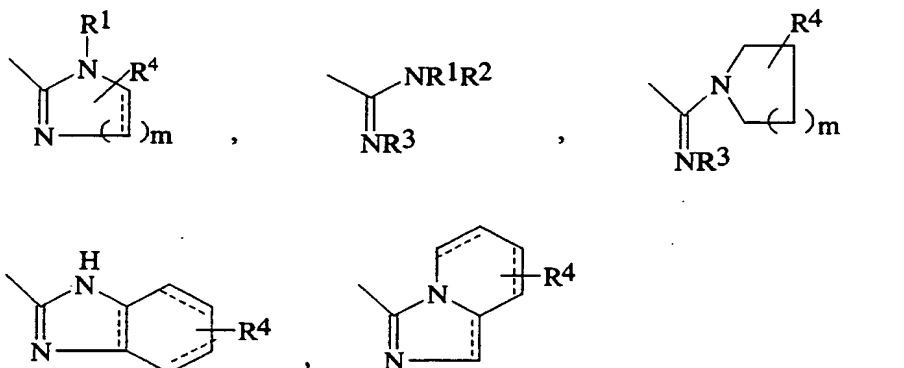


Ar² is an aryl moiety selected from the group consisting of phenyl, mono-, di-, and tri-substituted phenyl, wherein the substituents are selected from the group consisting of Cl, Br, F, CF₃, lower alkyl, lower alkoxy, NH₂, NO₂, and OH; Q is selected from the group consisting of:

- (i) -O-;
- (ii) -CH₂-;
- (iii) -OCH₂-;
- (iv) -CH₂O-;
- (v) -NH-;
- (vi) -NHCH₂-;
- (vii) -CH₂NH-;
- (viii) -CF₂-;
- (ix) -CH=CH-;
- (x) -CH₂CH₂-, and
- (xi) carbon-carbon single bond;

n is 1, 2, or 3; and

Z is



wherein

R^1 , R^2 and R^3 are independently H, OH, lower alkyl, lower alkoxy, allyl, cyclic alkyl or $(CH_2)_p-CO_2R^5$ wherein p is an integer from 1 to 6;

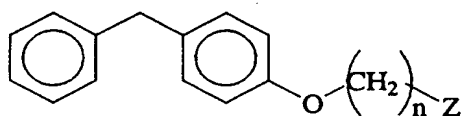
R^4 is H, CO_2R^5 , $CONH_2$, or $COOH$;

R^5 is H, lower alkyl, lower alkoxy, allyl or benzyl;

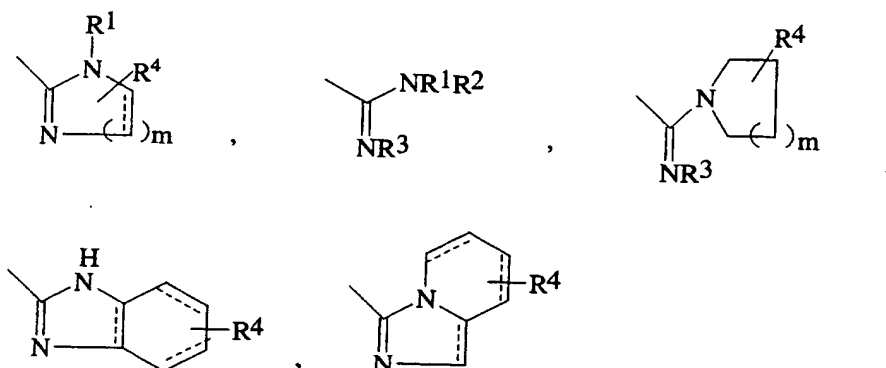
----- represents a single or double bond;

and m is 1 or 2.

34. The method of claim 33 wherein the compound has the structure:



wherein n is 1, 2, or 3 and Z is



wherein

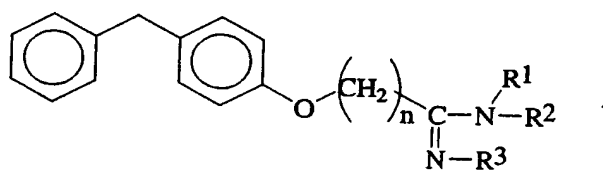
R^1 , R^2 and R^3 are independently H, OH, lower alkyl, lower alkoxy, allyl, cyclic alkyl or $(CH_2)_p-CO_2R^5$ wherein p is an integer from 1 to 6;

R^4 is H, CO_2R^5 , $CONH_2$, or $COOH$;

R^5 is H, lower alkyl, lower alkoxy, allyl or benzyl;

----- represents a single or double bond;
and m is 1 or 2.

35. The method of claim 34 wherein the compound has the structure:



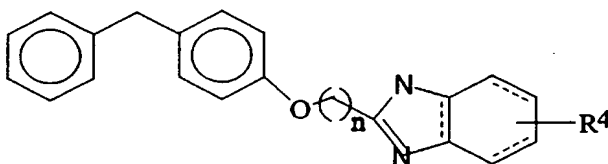
36. The method of claim 35 wherein in the compound R^2 is $(CH_2)_mCO_2R^5$.

37. The method of claim 36 wherein in the compound n is 1 and m is 2.

38. The method of claim 34 wherein in the compound R^1 and R^2 are independently hydrogen, lower alkyl, or cyclic alkyl.

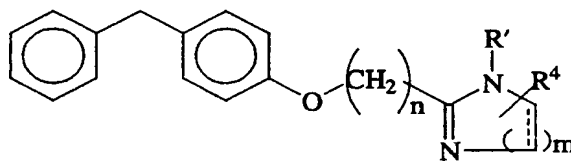
39. The method of claim 38 wherein in the compound R^3 is hydrogen or hydroxyl.

40. The method of claim 34 wherein the compound has the structure:



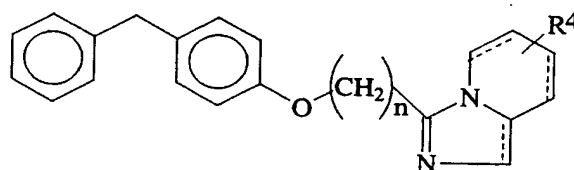
41. The method of claim 40 wherein in the compound R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

42. The method of claim 34 wherein the compound has the structure:



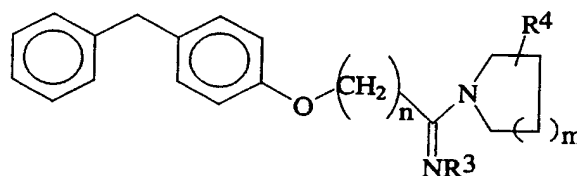
43. The method of claim 42 wherein in the compound R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

44. The method of claim 34 wherein the compound has the structure:



45. The method of claim 44 wherein in the compound R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

46. The method of claim 34 wherein the compound has the structure:



47. The method of claim 46 wherein in the compound R^3 is hydrogen or hydroxyl and R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

48. The method of claim 34 wherein the compound is chosen from the group consisting of:

α -[[4-(phenylmethyl)phenoxy]methyl]-1-piperidinemethanimine, monohydrochloride;

α -[[4-(phenylmethyl)phenoxy]methyl]-1-pyrrolidinemethanimine, monohydrochloride;

ethyl 1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidinecarboxylate, monohydrochloride;

ethyl 3-[[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]amino]propanoate, monohydrochloride;

4,5-dihydro-2-[4-(phenylmethyl)phenoxy]methyl]-1H-imidazole;

1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidinecarboxamide;

1-imino-2-[4-(phenylmethyl)phenoxy]ethanamine;

α -[3-[4-(phenylmethyl)phenoxy]propyl]-1-piperidinemethanimine, monohydrochloride;

4,5-dihydro-2-[3-[4-(phenylmethyl)phenoxy]propyl]-1H-imidazole;

3a,4,5,6,7,7a-hexahydro-2-[4-(phenylmethyl)phenoxy]propyl]-1H-benzimidazole;

2-[4-(phenylmethyl)phenoxy]-N-(tricyclo[3.3.1.1^{3,7}]decan-2-yl)ethanimidine, monohydrate;

N'-hydroxy-2-[4-(phenylmethyl)phenoxy]ethanimidamide.

INTERNATIONAL SEARCH REPORT

In. tional Application No
PCT/US 98/03927

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D295/08 C07D211/62 C07D233/18 C07D235/12 C07D233/10
C07C257/14 A61K31/445 A61K31/155

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| Y | WO 96 11192 A (SEARLE & CO ;CHANDRAKUMAR NIZAL SAMUEL (US); CHEN BARBARA BAOSHENG) 18 April 1996 see the whole document --- | 1-32 |
| Y | WO 96 10999 A (SEARLE & CO ;CHANDRAKUMAR NIZAL SAMUEL (US); CHEN BARBARA BAOSHENG) 18 April 1996 see the whole document --- | 1-32 |
| Y | DE 41 21 849 A (RHONE POULENC RORER GMBH) 14 January 1993 see the whole document --- | 1-32 |
| A | WO 96 41625 A (SEARLE & CO) 27 December 1996 see the whole document --- | 17 |
| -/-- | | |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

26 June 1998

Date of mailing of the international search report

09.07.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Fax: (+31-70) 340-3016

Authorized officer

Frelon, D

INTERNATIONAL SEARCH REPORT

In. tional Application No
PCT/US 98/03927

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|---|-----------------------|
| Category | Citation of document, with indication where appropriate, of the relevant passages | Relevant to claim No. |
| A | CHEMICAL ABSTRACTS, vol. 117, no. 11, 14 September 1992 Columbus, Ohio, US; abstract no. 111411, XP002068845 see abstract & R. LABAUDINIÈRE ET AL.: J. MED. CHEM., vol. 35, no. 17, 1992, pages 3156-3169, --- | 1-32 |
| A | CHEMICAL ABSTRACTS, vol. 126, no. 1, 1 January 1997 Columbus, Ohio, US; abstract no. 302, XP002068846 see abstract & J.H. YUAN ET AL.: DRUG METAB. DISPOS. , vol. 24, no. 10, 1996, pages 1124-1133, --- | 1-32 |
| X | CHEMICAL ABSTRACTS, vol. 53, no. 10, 25 May 1959 Columbus, Ohio, US; abstract no. 9194, XP002068847 see abstract & V.G. CAVALLINI ET AL.: FARMACO ED. SCI., vol. 11, 1956, PAVIA, pages 378-388, --- | 1,2,10 |
| X | EP 0 287 959 A (BASF AG) 26 October 1988 see page 77; example 30.1 ----- | 1,2,10 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 03927

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 33-48
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 33-48
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition (Rule 39.1 iv) PCT)
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 98/03927

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds which are encompassed by the general definition in the independent claims, the search had to be restricted for economic reasons. The search was limited to the prepared compounds for which pharmacological data are given (see Guidelines, Chapter III, paragraph 2.3). Additionally the rests R7, R8 and R9 are not defined and consequently no complete search could be made correspondingly.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ternational Application No

PCT/US 98/03927

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|--|--|
| WO 9611192 A | 18-04-1996 | US 5585492 A AU 3686595 A CA 2202371 A EP 0804427 A US 5719306 A | 17-12-1996 02-05-1996 18-04-1996 05-11-1997 17-02-1998 |
| WO 9610999 A | 18-04-1996 | AU 3686695 A CA 2202368 A EP 0786992 A US 5723492 A | 02-05-1996 18-04-1996 06-08-1997 03-03-1998 |
| DE 4121849 A | 14-01-1993 | NONE | |
| WO 9641625 A | 27-12-1996 | US 5700816 A AU 6274496 A EP 0843549 A | 23-12-1997 09-01-1997 27-05-1998 |
| EP 0287959 A | 26-10-1988 | DE 3713337 A DE 3803703 A CA 1331619 A DE 3880544 A ES 2054725 T JP 1063568 A JP 2534315 B KR 9610354 B MX 9203407 A SU 1655293 A US 4943584 A | 10-11-1988 17-08-1989 23-08-1994 03-06-1993 16-08-1994 09-03-1989 11-09-1996 30-07-1996 01-08-1992 07-06-1991 24-07-1990 |